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Applicants have amended the specification to correct the informalities noted by the Examiner, including the deposit number and SEQ ID NOs. A copy of the plasmid deposit receipt is provided herewith.

Applicants have amended the claims to recite that the nucleic acid molecules are isolated, and to recite SEQ ID NOs, where appropriate. Applicants also have amended claim 1 to recite a "% homology" limitation, based on the disclosure of such in the specification at page 5, line 21-25 and page 5, line 33 – page 6, line 6. No new matter has been added.

Applicants enclose herewith a certified copy of the priority document, GB 9828377.3, to perfect the priority claim under 35 U.S.C. 119. Acknowledgement of the priority claim is respectfully requested.

The Examiner noted that the Information Disclosure Statement filed by Applicants on February 9, 2001 (paper no. 7) was not considered for lack of submission of the cited references. Applicants cannot explain the lack of references in the Examiner's possession, as all of the cited references were filed as stated. To remedy the lack of references, and to allow the Examiner to consider the properly filed IDS of February 9, 2001, Applicants enclose herewith an additional set of copies of the references cited in the IDS. Applicants also enclose the transmittal sheet showing filing of cited references on February 9, 2001. Consideration of the previously filed IDS and cited references is respectfully requested.

Claim Objections

The Examiner objected to claims 1-4, 6, 7, 11, 12, 14, 15, 21, 30, 31, 39-44, 54-56 and 72. Applicants have amended the claims as needed to recite SEQ ID Nos. Claim 21 was amended to change dependency; this claim now depends only from claim 11. Claim 14 was canceled.

The Examiner objected to claim 42 as being a substantial duplicate of claim 40. Applicants respectfully disagree; although they refer to the same figure, these two claims are concerned with different sequences in the figure. Claim 40 refers to the amino acid sequence while claim 42 refers to the specific nucleotide sequence in Figure 26 that encodes the polypeptide having the CUB domain. Therefore the claims are not substantially identical because claim 42 is substantially narrower in scope than claim 40.

In view of the amendments to the claims and the argument regarding claims 40 and 42 set forth above, Applicants respectfully request that the Examiner withdraw the objections to the claims.

Rejections Under 35 U.S.C. 101

The Examiner rejected claims 1-4, 6, 7, 14, 30, 39-43, 54-56 and 72 under 35 U.S.C. 101 as directed to non-statutory subject matter. Applicants have amended the claims, where appropriate, to recite that the claimed nucleic acid molecules are "isolated." Accordingly, Applicants respectfully request that the Examiner withdraw the rejections of these claims under 35 U.S.C. 101.

Rejections Under 35 U.S.C. 112, First Paragraph

Enablement

The Examiner rejected claims 1-4, 6, 7, 11, 12, 14, 15, 21, 30, 31, 39-47, 54-56 and 72 under 35 U.S.C. 112, first paragraph, as not enabled. Applicants respectfully traverse the rejection.

The Examiner stated that the specification was enabling for nucleic acid molecules comprising SEQ ID NO:3, but not for variants thereof, for sequences identified by hybridization, or for sequences comprising functional domains. The Examiner states, for example, that Applicant "has not described the characteristics of the VEGF-X nucleic acid sequence so that one of skill in the art could predictably identify other sequence encoding VEGF-X molecules." Office Action at page 4.

Respectfully, Examiner's stated reasons for finding a lack of enablement are not relevant when the plain language of the claims is considered. The specification provides a detailed description of how to use the claimed invention, including a number of variants of the sequences set forth in SEQ ID NO:1 or SEQ ID NO:2. Applicants have amended claim 1 to recite that sequences with a defined percentage of homology are included in the scope of the claim.

A finding of non-enablement should be supported by a thorough analysis of all eight of the Wands factors. In re Wands 858 F 2d. 731, 737, 740, 8 U.S.P.Q. 2d 1400, 1404, 1407 (Fed.

Cir. 1988). In the case of the present invention, the Applicants believe that a full consideration of all eight of the Wands factors would favor a finding of enablement.

The Examiner focused solely on the first two Wands factors; 1) the quantity of experimentation necessary, and 2) the amount of direction or guidance presented.

Applicants do not agree with the Examiner's assertion that "...one of skill in the art would not predictably be able to use" the VEGF-X sequence. Office Action at page 5. According to the Examiner, undue experimentation results from a lack of adequate guidance as to "...what structural features would result in the particular characteristics of VEGF-X, and what sequences would conserve CUB function or allow VEGF-like function...." Office Action at page 5.

It should be noted that in the determination of what constitutes undue experimentation the "...test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed...." In re Wands at 737 citing In re Jackson, 217 U.S.P.Q. at 807.

Applicants respectfully disagree with the Examiner that to fully practice the scope of the invention the user requires additional guidance. The nature and quantity of experimentation necessary to practice the full scope of the invention is not undue or excessive. Any experimentation needed to practice the claimed invention is entirely routine and clearly falls within the scope of permissive experimentation as defined by Wands.

The Examiner did not consider the remaining Wands factors: 3) the presence or absence of working examples, 4) the nature of the invention, 5) the state of the prior art, 6) the relative skill of those in the art, 7) the predictability or unpredictability of the art, and 8) the breadth of the claims. Applicants contend that none of these requirements weigh against a finding of enablement.

With respect to the requirements of the third factor, Applicants have provided illustrative working examples to aid the skilled artisan in practicing the invention. Contrary to the Examiner's objection, the present application does indeed provide the necessary information to enable one skilled in the art to identify, make and use VEGF-X variants. More specifically, Figure 3 identifies specific primers which can be used to amplify VEGF-X sequence from cDNA and which is also identified on page 29, lines 16-17. Using these primers, VEGF-X positive

clones were identified from a cDNA library (Figure 4), all of which were sequenced and for some of them the corresponding sequence of the VEGF-X variant protein is shown in Figure 12 (see also page 32, lines 8-21). Furthermore, the genomic sequence of the VEGF-X gene is also provide in Figure 30; this figure identifies the intron/exon boundaries and the location of splice sites within the VEGF-X sequence. Therefore, it is submitted that then present application does indeed provide sufficient information to the skilled practitioner to identify further VEGF-X variants in addition to those specific amino acid and nucleotide sequences encoding VEGF-X and the splice variants identified in the specification.

Regarding the rejection of claims pertaining to CUB or VEGF-like domains, the specification on page 19, lines 3-5 characterizes the CUB domain as the N-terminal part of the VEGF-X protein. More particularly, it is specifically identified as being located from position 40-150 of VEGF-X sequence illustrated in Figure 10. The corresponding nucleotide sequence and the embodiment wherein the CUB domain may be included in an expression vector has been provided in Figure 26, which illustrates a DNA polynucleotide sequence used for *E. coli* expression of the CUB-like domain of VEGF-X. It was further demonstrated that the CUB domain inhibits proliferation of HUVECs. A cell proliferation assay to assess the growth inhibitory activity on HUVECs is described on page 41, line 15 through page 42, line 13. It would be expected that a polypeptide incorporating the CUB domain would function in the same manner and the creation and/or testing of such polypeptides, in view of the disclosure of the specification, would not require undue experimentation.

Regarding the VEGF domain, while no function has been demonstrated for the domain, it has been demonstrated that this domain is located toward the C-terminus of the protein as can be seen from the alignment with other VEGF molecules in Figure 11. The specification at page 34, lines 8-13 also discloses an *E. coli* expression vector comprising the VEGF domain as shown in Figure 24. The VEGF domain is known from other VEGF proteins as a potent vasoactive protein which is comprised of a glycosylated cationic 46-49 kDa dimer having two 24 kDa subunits. The latter has been confirmed for the VEGF domain of the VEGF-X protein as provided in the glycosylation assay on page 35 of the present application. Therefore tests or procedures to verify the functional characteristics of the VEGF domain like proteins are known to the skilled person.

As for the fourth factor, the nature of the claimed invention itself is such as to be readily understandable by anyone skilled in art as it pertains to nucleic acids encoding novel VEGF polypeptides, domains thereof and variants thereof.

Applicants contend that enablement of the claimed invention is further buttressed by the fact that the state of the art in molecular biology has advanced to the point that sequence manipulation as described in the specification has become routine in the field. At the time of the filing of the instant application in 1999, a skilled artisan could predictably use nucleic acid amplification and cloning to isolate, for example, VEGF-X splice variants.

With respect to the remaining factors, the present application bears similarity to Wands in that there was "a high level of skill in the art at the time the application was filed" and "all of the methods needed to practice the invention were well known". In re Wands 858 F.2d at 740, 8 U.S.P.Q.2d at 1406. Applicants contend that sufficient direction and guidance is provided, along with relevant working examples, to allow an artisan to successfully practice the claimed invention throughout its scope. Again, the field of molecular biology, at the time of the invention, was sufficiently advanced to allow one skilled in the art to either generate mutant polypeptides or isolate additional variants without requiring any additional methodological disclosures. Additionally, the predictability of the art of molecular biology at the time of filing was such that the skilled artisan could predictably utilize the aforementioned molecular biology techniques as taught in the application. The relevant standard for an enabling disclosure was set forth by the court in In re Howarth, "[i]n exchange for the patent, [the applicant] must enable others to practice his invention. An inventor need not, however, explain every detail since he is speaking to those skilled in the art." 654 F. 2d 103, 105 (C.C.P.A. 1981).

Accordingly, Applicants respectfully request that the Examiner withdraw the rejections made under 35 U.S.C. §112, first paragraph for lack of enablement.

Written Description

The Examiner rejected claims 1-4, 6, 7, 11, 12, 14, 15, 21, 30, 31, 39-47, 54-56 and 72 under 35 U.S.C. 112, first paragraph, as lacking an adequate written description. Applicants respectfully traverse the rejection.

As an initial matter, Applicants note that a variety of representative nucleic acid molecules have been provided in the specification, so that one of ordinary skill in the art can

readily envision that Applicants were in possession of the claimed invention. First, nucleic acid molecules that encode VEGF-X polypeptide are provided, as are additional related nucleic acid molecules that encode VEGF-X polypeptide, but differ in nucleotide sequence in accordance with the degeneracy of the genetic code. Second, Applicants have identified variants of the VEGF-X protein, such as splice variants, and have also provided methodologies for one of ordinary skill in the art to identify additional members of the genus. Therefore, Applicants maintain that a sufficiently representative number of VEGF-X variants were identified in the specification to provide an adequate written description of the claimed invention.

More generally, Applicants note that the basic requirement of the written description requirement is that the claimed invention must be described clearly enough to allow one of ordinary skill in the art to recognize that the inventors invented the claimed invention. *Vas-Cath v. Mahurkar* 935 F.2d 1555, 19 USPQ2d 1111 (Fed. Cir. 1991); *Lockwood v. American Airlines, Inc.* 107 F.3d 1565, 41 USPQ2d 1961 (Fed. Cir. 1997); *In re Gosteli* 872 F.2d 1008, 10 USPQ 2d 1614 (Fed. Cir. 1989). The requirement is based on the knowledge of the skilled artisan in the particular art: the applicant must convey to one of ordinary skill in the art through the disclosure in the invention that the applicant was in possession of the claimed invention. The court in *Pfaff v. Wells* stated that the invention must be described with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. *Pfaff v. Wells Electronics, Inc.*, 48 USPQ2d 1641,1646 (1998). A discussion of requisite identifying characteristics may be found in *Regents of the University of California v. Eli Lilly* 119 F.3d 1559, 43 USPQ 2d 1398 (Fed. Cir. 1997). The *Lilly* case states that a DNA molecule must be described by a precise definition, "such as by structure, formula, chemical name or physical properties." *Id.*

A genus of nucleic acid molecules is not routinely defined in the art by an exhaustive listing of sequences, chemical formulas or chemical names. Instead, the art routinely identifies groups of nucleic acid molecules by how homologous the members of the group are, such as by hybridization to a particular nucleotide sequence, or by recitation of a homology percentage. A percent homology recitation in combination with a reference sequence provides a precise definition of the claimed nucleic acid molecules, because it is a recitation of physical properties. This sort of identification describes the physical properties of a genus of nucleic acid molecules as surely as IR and MS spectra describe the physical properties of a set of chemical compounds.

As one of ordinary skill in the art would know, the claimed molecules must be sufficiently like the reference sequences (i.e., nucleic acid molecules that encode SEQ ID NO:1 or 2) to fit within the specifically defined percent homology. Because the person of ordinary skill in the art would recognize, in accordance with the standard practice in the art, that Applicants' invention includes a limited genus of nucleic acid molecules closely related by physical structure, thereby having the defined percent homology, and further would recognize that Applicants invented the claimed genus based on the description of the genus in the specification, Applicants have fulfilled the requirement of the law for providing an adequate written description of the claimed invention.

One of ordinary skill in the art can readily identify whether a particular sequence is part of the claimed genus by performing a simple and well-established comparison of sequence using the defined percent homology provided in the specification and the claims. Thus, because Applicants have provided an adequate written description of the claimed invention, one of ordinary skill in the art will be certain if a particular sequence is, or is not, part of the claimed genus.

Accordingly, Applicants respectfully request that the Examiner withdraw the rejections made under 35 U.S.C. §112, first paragraph for lack of an adequate written description.

Applicants respectfully request reconsideration of the claims in view of the amendments and reasoned statements made above. If the Examiner wishes to advance the prosecution, or if the amendment is defective or unclear, then the Examiner is invited to telephone the undersigned at the telephone number listed below.

Respectfully submitted,

By: John R. Van Amsterdam

John R. Van Amsterdam, Reg No. 40,212
Wolf, Greenfield & Sacks, P.C.
600 Atlantic Avenue
Boston, MA 02210
Telephone (617) 720-3500

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Marked-up Paragraphs of Specification

At page 21, lines 15-16:

Plasmid VEGF-X CUB

PET22b 20 December 1999 LMBP 3991 [------]

At page 22, lines 1-4:

Figure 3: is an illustration of PCT primer sequences (SEQ ID NOs:4-13) utilised to identify the VEGF-X protein according to the invention.

At page 22, lines 12-15:

Figure 5: is an illustration of the nucleotide sequences of the 5' RACE primers (SEQ ID NOs:14-17) used to identify the 5' end of the VEGF-X open reading frame.

At page 22, lines 32-34:

Figure 10: is an illustration of the predicted amino acid sequence (SEQ ID NO:2) of the nucleotide sequence of Figure 9. SEQ ID NO:1 is amino acids 23-345 of SEQ ID NO:2.

At page 53, lines 19-33:

Sequence ID No 14 corresponds to the polynucleotide sequence of VEGFX11 illustrated in Figure 5 [4].

Sequence ID No 15 corresponds to the polynucleotide sequence of VEGFX12 illustrated in Figure 5 [4].

Sequence ID No 16 corresponds to the polynucleotide sequence of VEGFX13 illustrated in Figure 5 [4].

Sequence ID No 17 corresponds to the polynucleotide sequence of VEGFX14 illustrated in Figure 5 [4].

Marked-up Claims

1.(amended) An isolated nucleic acid molecule encoding a VEGF-X protein [or a functional equivalent, derivative or bioprecursor thereof], said protein comprising [any of the sequences from position 23 to 345 of] the amino acid sequence [illustrated in Figure 10,] of SEQ ID NO:1 or SEQ ID NO:2, or an amino acid sequence that is at least 70% homologous to SEQ ID NO:1 or SEQ ID NO:2 [the complete sequence as illustrated in Figure 10].

2.(amended) An isolated nucleic acid molecule according to claim 1 wherein said nucleic acid is a DNA molecule.

3.(amended) An isolated nucleic acid molecule according to claim 1 wherein said nucleic acid is a cDNA molecule.

4.(amended) An isolated nucleic acid molecule according to claim 3 comprising the nucleotide sequence set forth as SEQ ID NO:3 [from position 257 to 1291 of the nucleotide sequence illustrated in Figure 9], or sequences that hybridise thereto under high stringency conditions or the complement thereto.

6.(amended) An isolated nucleic acid molecule according to claim 1 which is of mammalian origin.

7.(amended) An isolated nucleic acid molecule according to claim 6 which is of human origin.

11.(amended) An expression vector comprising an isolated nucleic acid molecule according to claim 1.

21.(amended) A process for producing a VEGF-X protein [according to claim 8], said process comprising transforming a host cell or organism with an expression vector according to claim 11, and recovering the expressed protein from said host cell or organism.

30.(amended) An isolated nucleic acid molecule [sequence] comprising [the] a nucleotide sequence[s illustrated in any] selected from the group consisting of SEQ ID NOs:4-25 [Figures 3, 5, 8 or 13].

39.(amended) An isolated nucleic acid molecule encoding a polypeptide having a CUB domain, said polypeptide comprising the amino acid sequence of SEQ ID NO:26 [from position 40 to 150 of the sequence of Figure 10].

40.(amended) An isolated nucleic acid molecule encoding a polypeptide having a CUB domain, said polypeptide comprising the amino acid sequence of [Figure 26] SEQ ID NO:27.

41.(amended) An isolated nucleic acid molecule according to claim 40, comprising the nucleotide sequence of SEQ ID NO:28 [from position 5 to 508 of the sequence illustrated in Figure 26].

42.(amended) An isolated nucleic acid molecule according to claim 41, comprising the nucleotide sequence of SEQ ID NO:29 [illustrated in Figure 26].

43.(amended) An isolated nucleic acid molecule encoding a VEGF like domain comprising the sequence [from position 214-345 of the sequence of Figure 10] of SEQ ID NO:30 or the sequence from position 15 to 461 illustrated in Figure 24.

44.(amended) An expression vector comprising an isolated nucleic acid molecule according to claim 39 or claim 40.

54.(amended) An isolated nucleic acid molecule encoding a polypeptide comprising a CUB domain having the sequence [from position 40 to 150 of the sequence of Figure 10] of SEQ ID NO:26 or SEQ ID NO:28 [from position 5 to 508 of the sequence of Figure 26] and a sequence encoding a VEGF domain.

55.(amended) An isolated nucleic acid molecule according to claim 54 wherein said sequence encoding said VEGF domain is selected from the sequences encoding any of VEGF A to D or isoforms or variants thereof.

56.(amended) An isolated nucleic acid molecule encoding a polypeptide comprising the amino acid sequence [from position 40 to 150 of the sequence of Figure 10] of SEQ ID NO:26 for use as a medicament.

72.(amended) An isolated nucleic acid molecule encoding a variant of a VEGF-X protein [having] comprising any of the sequences of nucleotides illustrated in Figure 12.